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Original Article

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Baseline risk of recurrence in stage I–II endometrial carcinoma

Shinsuke Sasada,[1,2] **Mayu Yunokawa**,[1,3] **Yae Takehara**,[1] **Mitsuya Ishikawa**,[4] **Shunichi Ikeda**,[4] **Tomoyasu Kato**,[4] **Kenji Tamura**[1]

[1]Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan
[2]Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan
[3]Department of Medical Oncology/Gynecologic Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan
[4]Department of Gynecology, National Cancer Center Hospital, Tokyo, Japan

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Correspondence to
Mayu Yunokawa
Department of Breast and Medical Oncology, National Cancer Center Hospital, 5 Chome-1-1 Tsukiji, Chuo-gu, Tokyo 104-0045, Japan.
E-mail: myunokaw@ncc.go.jp

ORCID iDs
Shinsuke Sasada
https://orcid.org/0000-0003-1623-869X
Mayu Yunokawa
https://orcid.org/0000-0001-7354-6977
Mitsuya Ishikawa
https://orcid.org/0000-0001-8855-2966
Tomoyasu Kato
https://orcid.org/0000-0001-9561-1522
Kenji Tamura
https://orcid.org/0000-0002-3514-9927

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Objective: Though there are no evidences that postoperative therapy improves overall survival (OS) in stage I–II endometrial carcinoma, many women receive postoperative radiation or chemotherapy. This study aimed to investigate the baseline risk of recurrence after complete resection without any adjuvant therapies and to suppose the validity of postoperative therapy for stage I–II endometrial carcinoma.
Methods: Charts for patients with stage I–II endometrial carcinoma who underwent operation without postoperative therapy between January 2005 and December 2011 were retrospectively reviewed and the baseline risk of recurrence and prognosis were assessed. Risk classifications were performed according to European Society for Medical Oncology (ESMO) clinical practice guidelines and Japanese guideline written by Japan Society of Gynecologic Oncology Group.
Results: Among 374 patients who underwent complete resection, 311 were evaluable. Five-year recurrence rates by ESMO and Japanese were 2.6% and 3.1% in low-risk, 9.2% and 6.6% in intermediate-risk and 13.5% and 13.8% in high-risk group (p=0.003 and 0.015, respectively). High-risk group had worse OS compared with low- and intermediate-risk groups (5-year OS, low: 97.9% and 97.6%, intermediate: 97.9% and 98.8%, and high: 89.5% and 87.5%; p=0.003 and 0.008, respectively). Independent predictive factors of recurrence were age over 60 years, type 2 (estrogen-independent) and peritoneal cytology.
Conclusion: ESMO and Japanese risk classification similarly stratify the baseline risk of recurrence. Patients with stage I–II endometrial carcinoma, especially low- and intermediate-risk diseases, have low recurrence rate and favorable OS, and the benefit of postoperative therapy might be small.

Keywords: Endometrial Neoplasms; General Surgery; Recurrence; Postoperative Care; Prognosis

INTRODUCTION

Carcinoma of corpus uteri are newly diagnosed in approximately 55,000 women and 10,000 succumb to death in the United States [1], and 10,000 are diagnosed and 2,000 succumb in Japan [2]. Stage classification of endometrial carcinoma are surgically determined and 5-year

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Conceptualization: S.S., Y.M., T.Y.; Data curation: S.S., T.Y.; Formal analysis: S.S.; Investigation: S.S., Y.M., T.Y.; Methodology: S.S., Y.M., K.T., T.K.; Project administration: Y.M., T.K.; Resources: I.M., I.S., K.T.; Software: S.S.; Supervision: K.T., T.K.; Validation: S.S.; Visualization: S.S.; Writing - original draft: S.S.; Writing - review & editing: Y.M., T.Y., I.M., I.S., K.T., T.K.

survival rates are 89.6% in stage I, 78.3% in stage II, 61.9% in stage III, and 21.1% in stage IV, respectively [3,4].

Adjuvant therapy is generally considered for patients with multiple prognostic factors identified for risk of recurrence. Several prescripts or guidelines define the categories for recurrence. European Society for Medical Oncology (ESMO) clinical practice guideline categorizes the risk of recurrence into low-, intermediate-, and high-risk groups by stage, tumor grade (G), and histologic subtype [5]. Japan Society of Gynecologic Oncology additionally incorporates lymphovascular space invasion (LVSI) into postoperative recurrence risk classification [6]. Adjuvant radiation therapy is common worldwide because it improves local control of early endometrial carcinoma [5]. In Japan, adjuvant chemotherapy is more usual, and more than half of women with the intermediate-risk disease and almost 90% with high-risk disease receive chemotherapy [7]. However, there is no precise evidence that radiotherapy or chemotherapy improves overall survival (OS) after surgery in stage I–II endometrial carcinoma.

Adjuvant therapy is performed for prevention of recurrence. Generally, it is decided considering the baseline risk of recurrence, risk reduction effect with additional treatment and toxicity. However, there is only a few data about detailed baseline risk of recurrence for patients without any adjuvant therapy because postoperative therapy has been conventionally performed. This study aims to grasp the baseline risk of recurrence and consider the validity of adjuvant therapy for early-stage endometrial carcinoma.

MATERIALS AND METHODS

1. Patients

Among patients with stage I–II endometrial carcinoma who underwent the operation between January 2005 and December 2011 at the National Cancer Center Hospital, the ones who met the following criteria were excluded: histological diagnosis of undifferentiated carcinoma, mixed epithelial and mesenchymal tumor and with neuroendocrine feature; other cancers in past 5 years (excluding carcinoma in situ); received adjuvant chemotherapy or radiotherapy; 30-days of mortality (**Fig. 1**). Surgical staging was performed using International Federation of Gynecology and Obstetrics (FIGO) 2009 staging [3]. Estrogen-dependent endometrial carcinoma (type 1) was defined as G1 and G2 endometrioid adenocarcinoma (EC), and

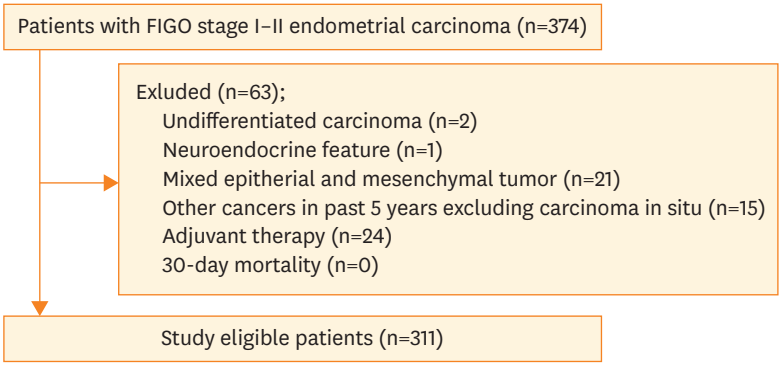

Fig. 1. Profile of this study.
FIGO, International Federation of Gynecology and Obstetrics.

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Table 1. Recurrence risk classification

Risk group	ESMO guidelines	Japanese guidelines
Low-risk	Stage IA (G1 and G2) with EC	Stage IA (G1 and G2) with EC LVSI negative
Intermediate-risk	Stage IA G3 with EC Stage IB (G1 and G2) with EC	Stage IA G3 with EC Stage IB (G1 and G2) with EC CCC and SC without myometrial invasion LVSI positive
High-risk	Stage IB G3 with EC All stages with non-EC Stage II*	Stage IB G3 with EC CCC and SC with myometrial invasion Stage II

CCC, clear cell adenocarcinoma; EC, endometrioid adenocarcinoma; ESMO, European Society for Medical Oncology; LVSI, lymphovascular space invasion; SC, serous adenocarcinoma.
*Stage II was categorized as high-risk in this study even though the ESMO clinical practice guidelines apply only to stage I disease.

estrogen-independent (type 2) as G3 or non-EC [8]. ESMO clinical practice guideline and Japanese guideline divide into 3 risk categories as **Table 1** [5,6]. In this study, stage II is subdivided into high-risk group though the classification of ESMO clinical practice guideline is for stage I. The Institutional Review Board (IRB) of the National Cancer Center Hospital approved this study (IRB No. 2015-259). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

2. Surgical procedure

All patients received at least abdominal total hysterectomy, bilateral salpingo-oophorectomy. Radical hysterectomy was performed for patients with suspicious cervical stromal invasion. Pelvic lymph node biopsy and para-aortic examination were performed in patients with G1/2 or inner half myometrial invasion diseases, and suspicious nodes were examined by rapid frozen section. Pelvic lymphadenectomy was applied for patients with outer-half myometrial invasion, G3 or non-EC. Pelvic and para-aortic lymphadenectomy were performed when lymph nodes metastasis has been recognized by preoperative examination, intraoperative findings or frozen section. Patients with histologically confirmed lymph node metastases were excluded from this study. Peritoneal lavage cytology was routinely performed. Omentectomy was carried out for patients with non-EC or positive peritoneal cytology.

3. Follow-up evaluation

All patients were followed up from the day of surgery. Postoperative follow-up procedures for the first 2 years comprised internal examination every 3 months and vaginal stump cytology as necessary. Thereafter, the patients were followed up every 6 months up to 5 postoperative years and computed tomography examination was assessed annually or when any abnormal findings were detected.

Patterns of failure were defined as follows; locoregional failure was defined as vaginal or intrapelvic recurrence. Distant recurrence included upper para-aortic lymph node metastasis, abdominal metastasis and metastasis to other organs.

4. Statistical analysis

Summarized data are presented as numbers and percentages unless otherwise stated. Frequencies were compared using Fisher's exact test for categorical variables. Predictors of recurrence were assessed by univariate and multivariate analyses using the Cox proportional hazards model. The patient population was subdivided based on cutoff for age derived from

receiver operating characteristic (ROC) curve. Cumulative recurrence incidence and OS were analyzed by the Kaplan-Meier method using the log-rank test. The OS was defined as the interval from the operation date to the death from any cause. If no events occurred, the last observation was censored. $p<0.05$ was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [9].

RESULTS

1. Patient characteristics

Among 374 patients who underwent complete resection, 311 patients were eligible and their characteristics are summarized in **Table 2**. The median age was 57 years. Patients with EC and stage Ia were common. Type 1 diseases were 251 (80.7%) and type 2 were 60 (19.3%). Patients with positive peritoneal cytology were 41 (13.2%). Patients with low/intermediate/high-risk diseases were 203/55/53 in ESMO clinical practice guideline and 174/93/44 in Japanese guideline, respectively.

2. Recurrence rate and survival

Recurrence rates were 4.8% in stage I and 17.6% in stage II, respectively. Recurrence rates according to FIGO staging and tumor grades were showed in **Table 3**. Only 5 patients (2.5%) recurred in stage Ia with G1 and G2 mainly meaning the low-risk group. According to analysis with recurrence risk categories, 5-year recurrence rates were 2.6%/3.1% in low-risk, 9.2%/6.6% in intermediate-risk, and 13.5%/13.8% in high-risk group by ESMO and Japanese

Table 2. Patient characteristics

Characteristic	No. (%)
Age (yr)	57 (28–88)
Menopausal status	
Premenopausal	85 (27.3)
Postmenopausal	226 (72.7)
Histology	
EC	278 (89.4)
SC	25 (8.0)
CCC	6 (1.9)
Mixed carcinoma	2 (0.7)
FIGO stage	
Ia	243 (78.1)
Ib	51 (16.4)
II	17 (5.5)
Tumor grade	
Grade1	181 (65.1)
Grade2	70 (25.2)
Grade3	27 (9.7)
Myometrial invasion	
Superficial	82 (26.4)
Inner half	170 (54.6)
Outer half	59 (19.0)
Lymphatic invasion	72 (23.2)
Vascular invasion	31 (10.0)
Peritoneal cytology positive	41 (13.2)

Values are presented as number (%) or median (range).
CCC, clear cell adenocarcinoma; EC, endometrioid adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; SC, serous adenocarcinoma.

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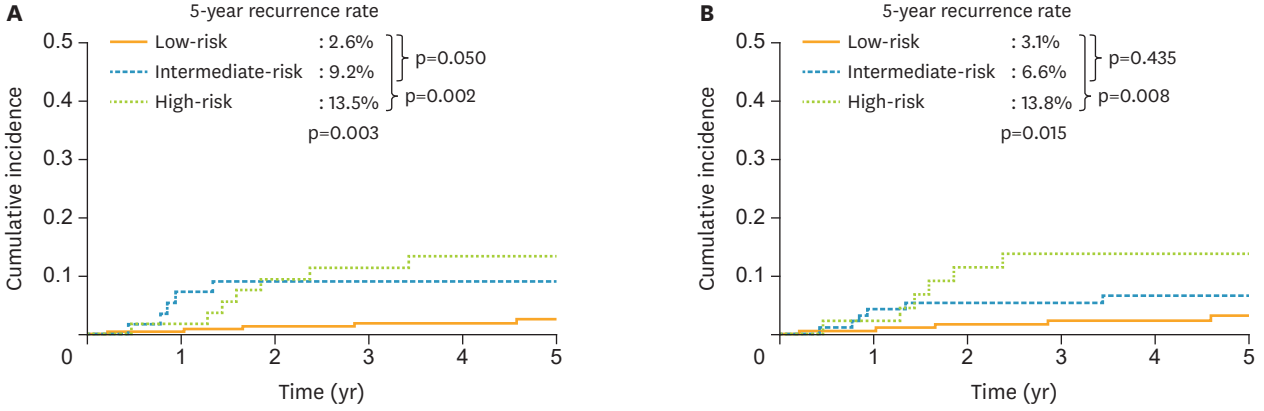
Table 3. Recurrence rates according to stage and tumor grade

Stage	G1 (n=181)	G2 (n=70)	G3 (n=27)	Non-EC (n=33)
Ia (n=243)	4/158 (2.5)	1/45 (2.2)	2/18 (11.1)	2/22 (9.1)
Ib (n=51)	2/20 (10.0)	1/17 (5.9)	1/8 (12.5)	1/6 (16.7)
II (n=17)	0/3 (0)	1/8 (12.5)	0/1 (0)	2/5 (40.0)

Values are presented as number (%).
EC, endometrioid adenocarcinoma; G, tumor grade.

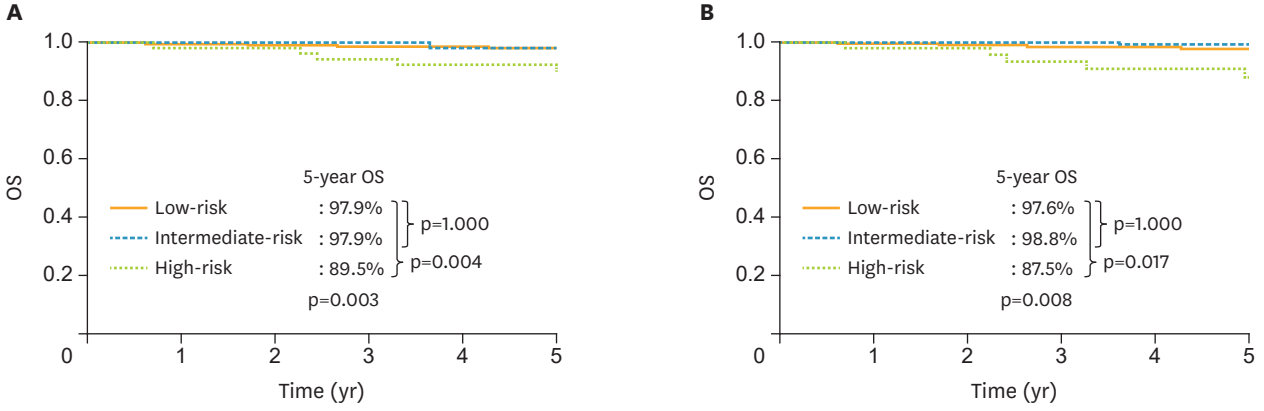
guidelines (p=0.003 and 0.015, respectively) (**Fig. 2**). Five-year OS rates were 97.9%/97.6% in low-risk, 97.9%/98.8% in intermediate-risk, and 89.5%/87.5% in high-risk group (p=0.003 and 0.008, respectively) (**Fig. 3**).



No. at risk						
Low-risk	203	202	200	196	181	138
Intermediate-risk	55	50	48	45	38	28
High-risk	53	52	46	44	40	30

No. at risk						
Low-risk	174	173	171	167	152	114
Intermediate-risk	93	88	85	82	74	56
High-risk	44	43	38	36	33	26

Fig. 2. Cumulative recurrence according to risk classification by the ESMO (A) and Japanese (B) guidelines.
ESMO, European Society for Medical Oncology.



No. at risk						
Low-risk	203	202	201	200	185	141
Intermediate-risk	55	54	52	50	43	33
High-risk	53	52	50	47	43	32

No. at risk						
Low-risk	174	173	172	171	156	117
Intermediate-risk	93	92	89	87	80	62
High-risk	44	43	42	39	35	27

Fig. 3. OSs according to risk classification by the ESMO (A) and Japanese (B) guidelines.
ESMO, European Society for Medical Oncology; OS, overall survival.

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3. Analysis of prognostic factors associated with recurrence

The ROC curve identified an optimal age cutoff value of 60 years for predicting the recurrence (area under the curve value of 0.717; 95% confidence interval [CI], 0.608–0.826). In multivariate Cox proportional hazard model, independent predictive factors of recurrence were over 60 years, type 2 disease and positive peritoneal cytology (**Supplementary Table 1**).

4. Recurrence sites

A total of 17 patients (9 in stage Ia, 5 in stage Ib, and 3 in stage II) experienced recurrence. Five, 9, and 3 patients had locoregional, distant, and locoregional plus distant recurrences, respectively. Areas of locoregional recurrences included the vagina (3) and pelvis (5); meanwhile, areas of distant recurrences included the peritoneum (3), liver (3), bone (3), lung (3), lymph node (3), and skin (1).

DISCUSSION

This study showed that stage I–II endometrial carcinoma had favorable prognosis without any adjuvant therapy. Notably, patients with low- and intermediate-risk disease had relatively low recurrence rate and excellent OS. ESMO and Japanese risk classification similarly stratified the baseline risk.

Several randomized clinical trials had been conducted to clarify the efficacy of adjuvant therapy. In stage III or IV endometrial carcinoma after surgery, Gynecology Oncology Group (GOG) 122 study demonstrated that doxorubicin and cisplatin chemotherapy significantly improved OS compared with whole-abdominal irradiation (hazard ratio [HR]=0.68; 95% CI=0.52–0.89; p<0.01) [10]. Patients with advanced endometrial cancer were recommended to receive adjuvant chemotherapy [5,6]. On the other hand, there is no clear evidence that demonstrates the survival advantage of adjuvant therapy for stage I and II disease. For patients with low-risk disease, adjuvant therapy is not recommended because their baseline risk of recurrence is very low (under 5%) and postoperative brachytherapy could not improve overall recurrence rate and survival [11]. For patients with intermediate-risk disease, such as stage I or II (occult disease) endometrial carcinoma, adjuvant external pelvic radiotherapy had been compared with observation [12-14]. Though they demonstrated that postoperative radiotherapy reduced locoregional recurrence, it could not improve OS. Two randomized clinical trials which compared between adjuvant radiotherapy and chemotherapy for the patients with stage Ic to IIIc disease could not confirm the superiority of any therapeutic strategies [15,16]. A combined analysis of 2 randomized studies of sequential adjuvant chemotherapy and radiotherapy comparing with radiotherapy showed that addition of adjuvant chemotherapy to radiation improved only progression-free survival (HR=0.63; 95% CI=0.44–0.89; p=0.009) [17]. However, there was no significant difference in OS (HR=0.69; 95% CI=0.46–1.03; p=0.07) and the subjects of these studies included approximately 20% of stage III.

Despite many clinical trials about adjuvant therapy for early-stage endometrial carcinoma, some problems remain. There was no trial which demonstrated the OS advantage of postoperative therapy compared with surgery alone. The effect of radiotherapy was limited to the prevention of locoregional recurrence and the benefit of chemotherapy was not confirmed compared with radiotherapy. In addition, when adjuvant chemotherapy was performed, the contribution of radiation for local control was unclear. Meanwhile,

the adverse effects of chemotherapy were common and the pelvic radiation therapy was associated with urinary and bowel symptoms, lower physical functioning and a reduction in quality of life [18,19]. In the clinical setting, however, the patients with intermediate- and high-risk early-stage endometrial carcinoma receive radiotherapy and/or chemotherapy after surgery. In Japan, chemotherapy is commonly performed for more than half of patients with intermediate-risk group and occasionally even for low-risk group [7]. The therapeutic strategy is determined considering the expected benefit and harm. The number needed to treat is an important indicator [20]. One previous report mentioned that the reduction rate of cancer death by chemotherapy was only 1% in low-intermediate risk disease [21]. The present study showed that the baseline recurrence risk of intermediate-risk disease was under 10% and 5-year OS was over 95%. A previous Japanese trial also found the locoregional recurrence rate after postoperative radiotherapy for intermediate- and high-risk endometrial carcinoma patients to be low (6.7%) compared to 12% in an Italian study [15,16]. These different recurrence rates between the 2 studies are presumably due to differences in the quality of surgical staging [22,23]. In situations where locoregional recurrence rates are low, the absolute risk reduction owing to adjuvant therapy is expected to be very small in the face of comparatively serious adverse events and economic burden.

On the other hand, we should select patients with early-stage disease which have worse prognosis and clarify the effect of adjuvant therapy for these patients. GOG 99 study and Japanese Gynecologic Oncology Group (JGOG) 2033 study investigated the prognosis of low- and high-intermediate risk subgroups. In high-intermediate risk group, GOG 99 study mentioned that adjuvant radiotherapy might reduce overall deaths than observation and JGOG 2033 study suggested that postoperative chemotherapy (cyclophosphamide/doxorubicin/cisplatin) conferred the survival benefit than radiotherapy [13,16]. The classifications of the postoperative recurrence risk were not identical in these reports. In this study, the subset analysis was performed to clarify the utility of the categorized subgrouping. The subset analysis of this study suggested the utility of the categorized subgrouping, especially by JGOG 2033 (**Supplementary Figs. 1** and **2**). The reason seems to be largely dependent on using strong variables such as age and peritoneal cytology. Recently, a new risk grouping to guide adjuvant therapy use was published by ESMO-European Society of Gynaecological Oncology (ESGO)-European Society for Radiotherapy and Oncology (ESTRO) consensus conference working group [24]. The classification newly proposed a high-intermediate risk group considering LVSI. Though adjuvant radiotherapy is recommended to decrease locoregional recurrence (recommendation grade B), the benefit of systemic therapy is uncertain (recommendation grade C) for high-intermediate risk endometrial carcinoma. In our study, 73 patients were high-intermediate risk by ESMO-ESGO-ESTRO classification, and 5-year recurrence rate was 6.9% and 5-year OS was 98.5% (**Supplementary Fig. 3**). We cannot conclude the necessity of Japanese specific risk grouping and high-intermediate risk group, but raise an alarm to the situation that adjuvant chemotherapy has been routinely performed for intermediate risk endometrial carcinoma in Japan.

The limitations of this study are associated with the retrospective nature in general and relatively small case size. In particular, only 17 patients (5.5%) had stage II endometrial carcinoma.

In conclusion, the present study clarified the baseline risk of recurrence and the prognosis of completely resected stage I–II endometrial carcinoma. In low- and intermediate-risk diseases, the recurrence rates were under 10% and the prognosis was favorable. Although a previously conducted Japanese trial failed to determine the

optimal chemotherapy regimen for intermediate- and high-risk endometrial carcinoma [25], the necessity of adjuvant chemotherapy for the intermediate-risk disease should be considered. A prospective randomized trial comparing between chemotherapy and observation (permitting vaginal brachytherapy) after surgery is essential and the European Organisation for Research and Treatment of Cancer (EORTC) 55102 trial (https://clinicaltrials.gov/ct2/show/NCT01244789) will be helpful.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Cox proportional progression hazard model for recurrence

Click here to view

Supplementary Fig. 1
Cumulative recurrence (A) and OS (B) of low- and high-intermediate risk groups by the GOG 99 study.

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Supplementary Fig. 2
Cumulative recurrence (A) and OS (B) of low- and high-intermediate risk groups by the JGOG 2033 study.

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Supplementary Fig. 3
Recurrence and OS according to new risk groups by ESMO-ESGO-ESTRO consensus conference.

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